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(19)

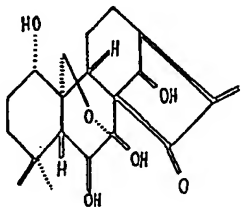
(54) PHARMACEUTICAL COMPOSITIONS HAVING ANTI-TUMOR ACTIVITY

(71) We, NIPPON SHINYAKU COMPANY LIMITED, of 14 Kisshoin Nishinosho Monguchicho, Minami-ku, Kyoto, Japan, a Company organised and existing under the laws of Japan, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

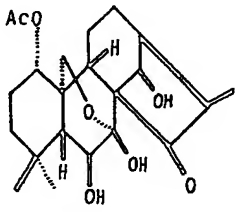
The present invention relates to pharmaceutical compositions having anti-tumor activity.

Accordingly the present invention is a pharmaceutical composition suitable for use as an anti-tumor agent which comprises oridonin and/or lasiokaurin and a solid or liquid carrier substance.

Oridonin and lasiokaurin are diterpenoids isolated from the *Isodon* plants of Labiatae, and their structures are shown as follows:—



Oridonin



Lasiokaurin

Oridonin was first isolated from the leaves of *Isodon japonicus* (Japanese name: Hikiokoshi) growing wild in Kochi district (Japan) and was shown to have m.p. 248—250° C (decompn) and $[\alpha]_D$-46°. Lasiokaurin was obtained from *Isodon lasiocarpus* (Japanese name: Taiwan-hikiokoshi) growing in Formosa and has m.p. 228—229° C and $[\alpha]_D^{17}$-94°. The structures and absolute configurations of these compounds have been elucidated by Fujita, one of the inventors, and his co-workers. See, for instance: E. Fujita, *et al., J. Chem. Soc (C)*, 1970, 1674—1681 and E. Fujita *et al., Chem. Pharm. Bull.* (Tokyo) *20*, 1752—1754 (1970).

The plants, *Isodon japonicus* and *I. trichocarpus* containing the oridonin or lasiokaurin in compounded or impure form, have been used as the bitter peptic in the home remedy, and reputed to be of marvellous efficacy for stomachache as well as gastrointestinal disorders. The investigation for the effective components, however, had little developed.

According to the present invention it has been found unexpectedly that the foregoing oridonin and lasiokaurin had a remarkable anti-tumor activity. The pharmacological experimental data of oridonin and lasiokaurin for anti-tumor activity are shown below.

The anti-tumor activity was assessed by injection of a solution of oridonin or lasiokaurin in 20% ethanol into the test animals. The male mice of ddY-strain (average body weight: 20±0.5 g) were used. Erlich ascites cell was inoculated into peritoneam of the mice, and the said tumor cells were adjusted to 2×10^6 cells/mouse. After 24 hours from inoculation, 0.25 ml of the foregoing solution or oridonin or laskiokaurin was injected intraperitoneally. Injection was repeated 7 times every 24

hours. These mice were observed for 40 days and the anti-tumor activity of oridonin and lasiokaurin was judged by comparison to the numbers of the dead mice with those of the control. The results are shown in the Table 1. The numerals in the table show percentage of the survival.

TABLE 1

Materials Given and Their Doses	Oridonin 5	Oridonin 10	Oridonin 15 mg./kg	Control	Lasiokaurin 10 mg./kg	Control
1	100%	100%	100%	100%	100%	100%
2	100	100	100	100	100	100
3	100	100	100	100	100	100
4	100	100	100	100	100	100
5	100	100	100	100	100	100
6	100	100	100	100	100	100
7	100	100	100	100	100	100
8	100	100	100	100	100	100
9	100	100	100	100	100	100
10	100	100	100	100	100	100
11	100	100	100	100	100	100
12	100	100	100	100	100	100
13	100	100	100	100	100	100
14	100	100	100	100	100	100
15	100	100	100	90	100	80
16	80	100	100	80	100	80
17	60	100	100	60	100	70
18	60	100	100	40	100	60
19	50	90	100	30	80	50
20	30	90	100	10	80	20
21	20	80	100	0	80	0
22	0	70	90	0	70	0
23	0	70	90	0	70	0
24	0	70	90	0	70	0
25	0	70	80	0	70	0
26	0	60	80	0	70	0
27	0	60	80	0	70	0
28	0	60	80	0	50	0
29	0	60	80	0	50	0
30	0	60	80	0	50	0
31	0	60	80	0	50	0
32	0	60	80	0	50	0
33	0	60	70	0	50	0
34	0	60	70	0	50	0
35	0	60	70	0	50	0
36	0	60	70	0	40	0
37	0	60	70	0	40	0
38	0	60	70	0	40	0
39	0	60	70	0	40	0
40	0	60	70	0	40	0
Mean Survival Days	18.0	32.4	35.5	17.1	30.4	17.6 days

Days Elapsed

As clarified by the foregoing experimental results, the dosage of 10 mg/kg and of 15 mg/kg of oridonin to mice showed the effect for survival time for 15.3 and 18.6 days on the average, respectively. Similarly, the dosage of 10 mg/kg of kasiokaurin to mice was effective for the prolongation of life for 12.8 days on the average. On the other hand, the experiments for the acute toxocity to mice (by intraperitoneal injection) gave 35—40 mg/kg as the LD_{50} value for oridonin and more than 70 mg/kg for lasiokaurin. These values are much larger than the foregoing effective doses. Oridonin and lasiokaurin are, therefore, safe and effective anti-tumor agents.

For the human body, oral administration, injection or other routes can be used. In the case of oral administration, the compounds are used as powders or tablets mixed with non-toxic carriers, e.g. milk sugar (lactose) starch (dextrin) etc. or as solution or emulsion. The dose may change depending on the condition and age of the patient.

These compounds dissolved in water, ethyl alcohol or mixtures of alcohol and water are used also as injection. In this case, some solubilizer may be added at need. The solution thus prepared, the patient is dosed by means of an intraperitoneal or intravenous injection. The dosage may change in compliance with the condition and age of the patient.

This invention, thus, provides the new and useful anti-tumor agents which show an excellent effect for the prolongation of survival in the Ehrlich ascites tumor-inoculated mice and are expected to be effective for several other tumors including cancer.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition suitable for use as an anti-tumor agent which comprises oridonin and/or lasiokaurin and a solid or liquid carrier substance.

2. A pharmaceutical composition as claimed in Claim 1 wherein the solid or liquid carrier substance is selected from milk sugar (lactose) starch (dextrin), water, ethyl alcohol and mixtures thereof.

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